



Clinical trial results:

A Phase 3, Open-label, Multicenter, Randomized Study of Sequential Zevalin (ibritumomab tiuxetan) versus Observation in Patients at least 60 Years of Age with Newly Diagnosed Diffuse Large B-cell Lymphoma in PET-negative Complete Remission after R-CHOP or R-CHOP-like Therapy

Summary

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2011-004916-51 |
| Trial protocol | GB IE IT ES BE PT NL AT DE FR |
| Global end of trial date | 23 October 2014 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 15 August 2020 |
| First version publication date | 15 August 2020 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | SPI-ZEV-11-301 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01510184 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Spectrum Pharmaceuticals, Inc. |
| Sponsor organisation address | 157 Technology Drive, Irvine, United States, |
| Public contact | Phil Stevens, Acrotech Biopharma LLC., pstevens@acrotechbiopharma.com |
| Scientific contact | Phil Stevens, Acrotech Biopharma LLC., pstevens@acrotechbiopharma.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 24 September 2015 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|-----------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 23 October 2014 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

Determine the efficacy and safety of the Zevalin study regimen compared to the 'Observation' arm in elderly patients in PET-negative complete response as defined by the Revised Response Criteria for Malignant Lymphoma, after first line R-CHOP or R-CHOP-like regimen.

Protection of trial subjects:

This protocol was conducted in accordance with the applicable Good Clinical Practices (GCP) regulations and guidelines, and in compliance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, and South Africa), ICH guidelines, or with the laws and regulations of the country in which the research was conducted.

An independent data monitoring committee (IDMC) was established for the purpose of reviewing patient safety and efficacy data. The IDMC was responsible for recommending whether the study should continue or stop early due to futility or safety concerns.

Background therapy:

Standard of care R-CHOP chemotherapy administered to patients prior to enrolment in the protocol.

Evidence for comparator:

Approximately 50-60% of patients presenting with DLBCL can be cured with a doxorubicin-based combination chemotherapy. Since the 1970s, CHOP has been the standard first-line therapy for patients with stage II-IV DLBCL. The CHOP regimen (cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² up to a maximum of 2 mg on day 1, and prednisone 40 mg/m²/day on days 1 to 5 every three weeks) is usually given for 6 or 8 cycles. Numerous studies have been performed during the last decades in an attempt to find chemotherapy regimens that are superior to CHOP alone. No alternative chemotherapeutic regimen has consistently shown improved results.

The addition of rituximab, an anti-CD20 monoclonal antibody improved outcomes in DLBCL. Superior results have been shown in elderly patients with a standard CHOP regimen to which rituximab was added (R-CHOP). This multicenter, randomized, clinical trial showed for all patients (including non-responders) a median 2-year OS rate of 70% in the R-CHOP patients, compared with 57% in the CHOP arm. This study was the basis for the EU approval of rituximab (375 mg/m²) to be given in combination with standard CHOP in patients with DLBCL over 60 years of age. An update after a median follow-up of 5 years, demonstrated a relapse rate of 20% and a 5-year OS rate of 58% for the R-CHOP arm, which supports the concept that unrealized minimal residual disease exists in patients despite achieving a CR/CRu.

In this study patients in the observation arm must have received 6 cycles of R-CHOP or R-CHOP-like treatment to be eligible.

| | |
|---|--------------|
| Actual start date of recruitment | 01 June 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Portugal: 1 |
| Country: Number of subjects enrolled | United Kingdom: 9 |

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Belgium: 1 |
| Country: Number of subjects enrolled | France: 4 |
| Country: Number of subjects enrolled | Ireland: 5 |
| Country: Number of subjects enrolled | Italy: 7 |
| Country: Number of subjects enrolled | Australia: 2 |
| Country: Number of subjects enrolled | United States: 43 |
| Country: Number of subjects enrolled | Canada: 1 |
| Country: Number of subjects enrolled | Israel: 6 |
| Worldwide total number of subjects | 79 |
| EEA total number of subjects | 27 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 77 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

A total of 79 patients were recruited across 10 countries.

Pre-assignment

Screening details:

Patient eligibility during the trial was assessed according to the eligibility criteria within the current version of the protocol at the time the patient was enrolled.

Pre-assignment period milestones

| | |
|------------------------------|----|
| Number of subjects started | 79 |
| Number of subjects completed | 79 |

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

Not applicable

Arms

| | |
|------------------------------|-----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Zevalin treated |

Arm description:

Patients receive rituximab on day 1 followed by rituximab on Days 7-9, and Y-90-Zevalin 4 hours later.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Zevalin |
| Investigational medicinal product code | PRD17186 |
| Other name | |
| Pharmaceutical forms | Kit for radiopharmaceutical preparation |
| Routes of administration | Intravenous use |

Dosage and administration details:

One administration of Zevalin on Day 7-9.

Days 7-9: Rituximab 250 mg/m² intravenous infusion, followed 4 hours later by Y-90-Zevalin 0.4 mCi/kg 10-minute intravenous push (0.3 mCi/kg in patients with a platelet count in 100,000/ μ L to 149,000/ μ L).

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | PRD00304MIG |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Single treatment on Day 1 and Day 7-9.

Day 1: Rituximab 250 mg/m² intravenous infusion.

Days 7-9: Rituximab 250 mg/m² intravenous infusion, followed 4 hours later by Y-90-Zevalin.

| | |
|------------------|-------------|
| Arm title | Observation |
|------------------|-------------|

Arm description:

Patients receive standard of care treatment i.e. R-CHOP or R-CHOP like therapy.

| | |
|----------|-----------------|
| Arm type | No intervention |
|----------|-----------------|

| Number of subjects in period 1 | Zevalin treated | Observation |
|--|------------------------|--------------------|
| Started | 36 | 43 |
| Completed | 0 | 0 |
| Not completed | 36 | 43 |
| Trial closure | 28 | 28 |
| Disease progression | 1 | 2 |
| Patient withdrawal | 1 | 4 |
| Lost to follow-up | - | 8 |
| Bone marrow positive for DLBCL after randomization | - | 1 |
| Lost to follow-up | 6 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------------------|
| Reporting group title | Overall study (overall period) |
|-----------------------|--------------------------------|

Reporting group description: -

| Reporting group values | Overall study (overall period) | Total | |
|---|-----------------------------------|-------|--|
| Number of subjects | 79 | 79 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Adults (59-85 years) | 79 | 79 | |
| Age continuous | | | |
| Units: years | | | |
| median | 70 | | |
| full range (min-max) | 59 to 85 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 42 | 42 | |
| Male | 37 | 37 | |
| Race | | | |
| Units: Subjects | | | |
| White | 73 | 73 | |
| Asian | 1 | 1 | |
| Black | 1 | 1 | |
| Other | 2 | 2 | |
| Unknown | 2 | 2 | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Not Hispanic or Latino | 73 | 73 | |
| Hispanic or Latino | 4 | 4 | |
| Not reported | 2 | 2 | |
| ECOG | | | |
| Units: Subjects | | | |
| 0-Fully active | 46 | 46 | |
| 1-Restricted | 31 | 31 | |
| 2-Ambulatory | 2 | 2 | |

End points

End points reporting groups

| | |
|--|-----------------|
| Reporting group title | Zevalin treated |
| Reporting group description: Patients receive rituximab on day 1 followed by rituximab on Days 7-9, and Y-90-Zevalin 4 hours later. | |
| Reporting group title | Observation |
| Reporting group description: Patients receive standard of care treatment i.e. R-CHOP or R-CHOP like therapy. | |

Primary: Overall survival

| | |
|---|---------------------------------|
| End point title | Overall survival ^[1] |
| End point description: The analysis description was further differentiated into 'living patients' and 'patients who died' in both the Zevalin and Observation arms. The median Overall Survival for living patients treated with Zevalin (8.9 months) was numerically greater than for patients in the Observation group (6.1 months). This was also true for the one patient who died in the Zevalin group (16.8 months) and the two patients in the Observation group (5.8 months). | |
| End point type | Primary |
| End point timeframe: Overall survival as defined by the time between date of randomisation and death of patient due to any cause | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Study terminated early for business reasons and the primary efficacy analysis could not be completed due to incomplete enrolment. All analysis was descriptive.

| End point values | Zevalin treated | Observation | | |
|-------------------------------|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 ^[2] | 43 ^[3] | | |
| Units: months | | | | |
| median (full range (min-max)) | | | | |
| Living patients | 8.9 (2.7 to 22.6) | 6.6 (0.07 to 21.3) | | |
| Patients who died | 16.8 (16.8 to 16.8) | 5.8 (1.9 to 9.7) | | |

Notes:

[2] - living patients = 35 + patients who died = 1

[3] - living patients = 41 + patients who died = 2

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From consent of the patient to Day 90 all adverse events were collected. From Day 91 only adverse events related to study treatment were collected.

Adverse event reporting additional description:

Safety population was used in all analyses of safety. Safety data of patients who received any study treatment was compared to safety data of patients who received no study treatment.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

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|--------------------|----|
| Dictionary version | 21 |
|--------------------|----|

Reporting groups

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|-----------------------|---------|
| Reporting group title | Zevalin |
|-----------------------|---------|

Reporting group description:

All randomized patients who received any element of Zevalin treatment including rituximab were classified in to the Zevalin treatment regimen arm.

| | |
|-----------------------|-------------|
| Reporting group title | Observation |
|-----------------------|-------------|

Reporting group description:

Patients randomised to the observation arm who did not receive any further anti-lymphoma therapy unless they had a relapse of their disease

| Serious adverse events | Zevalin | Observation | |
|---|-----------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 36 (22.22%) | 3 / 43 (6.98%) | |
| number of deaths (all causes) | 0 | 2 | |
| number of deaths resulting from adverse events | 0 | 2 | |
| Investigations | | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypotension | | | |

| | | | |
|--|-----------------|----------------|--|
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 43 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depressed Level of Consciousness | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 43 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 1 / 43 (2.33%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 43 (4.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |

| | | | |
|---|----------------|----------------|--|
| Infections and infestations | | | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | Zevalin | Observation | |
|---|------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 21 / 36 (58.33%) | 14 / 43 (32.56%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Seborrhoeic keratosis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 43 (2.33%) | |
| occurrences (all) | 0 | 1 | |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Flushing | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Embolism | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 43 (2.33%) | |
| occurrences (all) | 0 | 1 | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 43 (2.33%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 10 / 36 (27.78%) | 2 / 43 (4.65%) | |
| occurrences (all) | 15 | 2 | |
| Oedema | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pain | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Secretion discharge | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 43 (2.33%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 0 / 43 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 43 (2.33%) | |
| occurrences (all) | 0 | 1 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Investigations | | | |

| | | | |
|--|-----------------------|---------------------|--|
| Platelet count decreased subjects affected / exposed occurrences (all) | 6 / 36 (16.67%) 11 | 0 / 43 (0.00%) 0 | |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 6 / 36 (16.67%) 13 | 0 / 43 (0.00%) 0 | |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 6 / 36 (16.67%) 11 | 0 / 43 (0.00%) 0 | |
| Lymphocyte count decreased subjects affected / exposed occurrences (all) | 4 / 36 (11.11%) 13 | 0 / 43 (0.00%) 0 | |
| Blood potassium decreased subjects affected / exposed occurrences (all) | 1 / 36 (2.78%) 1 | 0 / 43 (0.00%) 0 | |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 1 / 36 (2.78%) 1 | 0 / 43 (0.00%) 0 | |
| Cardiac disorders | | | |
| Bradycardia subjects affected / exposed occurrences (all) | 1 / 36 (2.78%) 1 | 0 / 43 (0.00%) 0 | |
| Palpitations subjects affected / exposed occurrences (all) | 1 / 36 (2.78%) 1 | 0 / 43 (0.00%) 0 | |
| Sinus bradycardia subjects affected / exposed occurrences (all) | 0 / 36 (0.00%) 0 | 1 / 43 (2.33%) 1 | |
| Nervous system disorders | | | |
| Headache subjects affected / exposed occurrences (all) | 3 / 36 (8.33%) 3 | 0 / 43 (0.00%) 0 | |
| Dizziness subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 2 | 1 / 43 (2.33%) 1 | |
| Dysgeusia | | | |

| | | | |
|--------------------------------------|-----------------|----------------|--|
| subjects affected / exposed | 2 / 36 (5.56%) | 0 / 43 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Disturbance in attention | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 43 (2.33%) | |
| occurrences (all) | 2 | 1 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 3 / 43 (6.98%) | |
| occurrences (all) | 0 | 3 | |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 6 / 36 (16.67%) | 0 / 43 (0.00%) | |
| occurrences (all) | 15 | 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 1 / 43 (2.33%) | |
| occurrences (all) | 9 | 1 | |
| Anaemia | | | |
| subjects affected / exposed | 5 / 36 (13.89%) | 0 / 43 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Eye disorders | | | |
| Lacrimation increased | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 43 (2.33%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal disorders | | | |

| | | | |
|--|-----------------|----------------|--|
| Constipation | | | |
| subjects affected / exposed | 5 / 36 (13.89%) | 0 / 43 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Nausea | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 1 / 43 (2.33%) | |
| occurrences (all) | 6 | 1 | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 3 / 43 (6.98%) | |
| occurrences (all) | 5 | 4 | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 0 / 43 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 43 (2.33%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 0 / 43 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Blister | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dermal cyst | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dermatitis bullous | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Renal and urinary disorders | | | |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 43 (2.33%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 0 / 43 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 2 / 43 (4.65%) | |
| occurrences (all) | 3 | 3 | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Jaw disorder | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 43 (2.33%) | |
| occurrences (all) | 0 | 1 | |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 43 (2.33%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal pain | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 36 (0.00%) 0 | 1 / 43 (2.33%) 1 | |
| Infections and infestations | | | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 43 (2.33%) | |
| occurrences (all) | 0 | 1 | |
| Localised infection | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 43 (2.33%) | |
| occurrences (all) | 0 | 1 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 43 (2.33%) | |
| occurrences (all) | 0 | 1 | |
| Skin bacterial infection | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 43 (2.33%) | |
| occurrences (all) | 0 | 1 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pseudohyperkalaemia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 43 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypercalcaemia | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 43 (2.33%) | |
| occurrences (all) | 0 | 1 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 43 (2.33%) | |
| occurrences (all) | 0 | 1 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 43 (2.33%) | |
| occurrences (all) | 0 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|---|
| 14 March 2012 | <p>Summary of significant changes as follows:</p> <ul style="list-style-type: none">• Study population – utilisation of official name of response criteria in study; bone marrow cellularity of >15% is only required for those patients randomised to Zevalin. <p>Clarification to Methodology including:</p> <ul style="list-style-type: none">• Definition of risk groups• patient population• length of follow-up for safety assessment,• steps in the study,• response criteria to be used in study,• eligibility criteria,• inclusion and exclusion criteria,• description of patient number assignments made which include rationale for inclusion of follicular lymphoma grade 3B• randomisation process prior to study treatment• timeframe for collection of concomitant medications• timing for screening activities• timing of bone marrow biopsy to confirm complete remission• screening procedures relating to pathology reports and secondary pathology review• Age-adjusted International Prognostic Index• Post-randomisation study procedures for both arms• Evaluation and timing of disease status, including use of MRI and applicability of neck imaging• Follow-up activities• Timing of survival follow-up• Secondary pathology confirmation procedures• Extended screening window for physical exams• Handling of abnormal laboratory values as adverse events• Timing of haematology laboratory testing• Electrolytes measures in serum laboratory testing• Timing of serum chemistry laboratory testing• Changes to study procedures• Method of assessing disease status• Occurrence of secondary malignancies regardless of timing and study arm reported as SAE• Collection of AEs• Timing and reporting of SAEs to Sponsor• Stratification |

| | |
|-------------------|--|
| 30 September 2012 | <p>Summary of significant changes as follows:</p> <ul style="list-style-type: none"> • WHO classification 2008, as opposed to Revised European American Lymphoma used for confirmatory pathology review • Results updated for zevalin-randomised patients with the most current safety data • Zevalin Regimen scheduled to begin within 12 weeks of first day of last cycle of R-chemotherapy in line with Cheson 2007 response criteria <p>Changes to inclusion criteria:</p> <ul style="list-style-type: none"> - Confirmatory review was based on secondary reviews - H&E routine stain used for diagnostic purposes - Diagnostic CT scans performed 8 weeks after the first dose of the last cycle of R-chemotherapy. - PET-CT scans carried out in line with Cheson 2007 response criteria - Changes to blood counts monitored in line with standard practice <p>Changes to exclusion criteria including addition of pregnant and breastfeeding women and clarification of selection criteria</p> <ul style="list-style-type: none"> • Changes to randomisation criteria in line with Cheson 2007 response criteria • Preparation and release of IMP to be carried out in line with local guidelines and current standard practice • Concomitant therapy updated with the current safety information • Clarification of study and screening procedures in line with Cheson 2007 response criteria • Clarification of study procedures in line with Zevalin regimen patients and evaluation of remission status • Clarification of secondary pathology confirmation • Clarification of screening activities • Change in duration of follow-up of study activities until relapse • Clarification of safety risks in relation to reproductive risks |
|-------------------|--|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Study terminated early for business reasons and the primary efficacy analysis could not be completed due to incomplete enrolment.

Notes: